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RESEARCH ARTICLE

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A simple MALDI target plate with channel design to improve detection sensitivity and reproducibility for quantitative analysis of biomolecules

Zhen Liu[1] | Peng Zhang[2] | Lars Kästner[3] | Dietrich A. Volmer[4]

[1] Institute of Bioanalytical Chemistry, Saarland University, Saarbrücken, Germany

[2] School of Materials Science and Engineering, Sun Yat-sen University, Guanghzou, China

[3] Department of Anatomy and Cell Biology, Saarland University, Homburg, Germany

[4] Department of Chemistry, Humboldt University of Berlin, Berlin, Germany

Correspondence
Prof. Dr. Dietrich A. Volmer, Department of Chemistry, Humboldt University of Berlin, Brook-Taylor-Str. 2, Berlin 12489, Germany.
Email: dietrich.volmer@hu-berlin.de

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Abstract

Overcoming the detrimental effects of sweet spots during crystallization is an important step to improve the quantitative abilities of matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. In this study, we introduce MALDI targets, which exhibit a channel design to reduce sweet spot phenomena and improve reproducibility. The size of the channels was 3.0 mm in length, 0.35 mm in depth, and 0.40 mm in width, adjusted to the width of the implemented laser beam. For sample deposition, the matrix/sample mixture was homogenously deposited into the channels using capillary action. To demonstrate the proof-of-principle, the novel plates were used for the quantification of acetyl-L-carnitine in human blood plasma using a combined standard addition and isotope dilution method. The results showed that the reproducibility of acetyl-L-carnitine detection was highly improved over a conventional MALDI-MS assay, with RSD values of less than 5.9% in comparison with 15.6% using the regular MALDI method. The limits of quantification using the new plates were lowered approximately two-fold in comparison with a standard rastering approach on a smooth stainless-steel plate. Matrix effects were also assessed and shown to be negligible. The new assay was subsequently applied to the quantification of acetyl-L-carnitine in human plasma samples.

KEYWORDS

acetyl L carnitine, channel plates, MALDI-MS, plasma, quantification

1 | INTRODUCTION

During the sample preparation for MALDI-MS, the analytes are co-crystalized with a chemical matrix such as α-cyano-4-hydroxycinnamic acid (CHCA) or 2,5-dihydroxybenozic acid (DHB). Because of commonly observed heterogenous co-crystallization of matrix and analytes, ion signals usually fluctuate strongly from laser shottoshot and from sample spottospot, as dried matrix/analyte mixtures form sweet spots on the sample targets. MALDI-MS is therefore often dismissed as a quantitative technique.

There are, however, multiple methods to improve the reproducibility of MALDI-MS to levels similar to LC-MS techniques.[1,2] For example, using an internal standard for the analytes that matches solution phase and ionization properties has been shown to strongly improve reproducibility.[3-5] The obvious choices for this purpose are stable isotope standards, but unfortunately, often these standards are not

commercially available or very expensive. Alternatively, methods that improve the sample preparation procedures to force a homogenous distribution of matrix and analytes have been shown to significantly improve signal homogeneity. Methods that achieve these homogenous crystallizations include hydrophobic target coatings,[6,7] fast evaporation methods,[8] electrospraying techniques,[9,10] or seed layer approaches.[11,12] In addition, Zenobi and coworkers developed a self-aliquoting microarray plate that contains parallel lanes of hydrophilic reservoirs into which the samples were deposited using a metal sliding device. These arrays reduced sample requirements to just 10 µL per aliquot and exhibited excellent quantitative abilities, as demonstrated for angiotensin II and [Glu[1]] fibrinopeptide B.[13] Finally, large-area graphene films were used as target surface to improve reproducibility of matrix/analytes preparation for quantification of biomolecules in MALDI-MS.[14]

The downside of many of these techniques is that they require specialized hardware and that they are not as simple and convenient to use as conventional metal target plates. In this article, we describe a simple channel plate design to improve the reducibility of MALDI quantification, by forcing the matrix/analyte to dry within a narrowly confined cuboid of a few microliter internal volume on the steel target plates and subsequent scanning of the entire crystallized area using the MALDI laser beam. The quantitative abilities of this design were demonstrated for the analysis of acetyl-L-carnitine in human blood plasma matrices.

2 | EXPERIMENTAL

2.1 | Chemicals and materials

CHCA (alpha-cyano-4-hydroxycinnamic acid), acetyl-L-carnitine, and d_3-acetylcarnitine were purchased from Sigma-Aldrich (Steinheim, Germany); trifluoroacetic acid (TFA) was from Fisher Scientific (Schwerte, Germany); acetonitrile, methanol, and isopropanol were from VWR (Darmstadt, Germany). Deionized water was generated by a Millipore (Bedford, Massachusetts) water purification system.

2.2 | Blood plasma samples

Human plasma was prepared from blood samples from two healthy volunteers (with ethical permission, local research ethics committee, Ärztekammer des Saarlandes, ref. no. 51/18).

2.3 | Sample preparation

CHCA was prepared in methanol (TFA, 0.1% v/v) at 10 mg/mL. Acetyl-L-carnitine and d_3-acetyl-L-carnitine were dissolved in water at 1mM as stock solutions. All stock solutions were stored at −20°C and diluted to the required concentration prior to use.

Samples were prepared from 100 µL of plasma and 100 µL of internal standard solution (20.00 µM). To this mixture, 5 mL of acetonitrile/methanol (3:1 v/v) were added, and the combined mixture vortexed for 10 seconds, followed by centrifugation at 13 000 rpm (5 min); the supernatant was transferred into a new plastic tube. Centrifugation was repeated once more, and the combined supernatants were evaporated under vacuum in a homemade system; 100 µL of water was added, followed by vortexing for 5 minutes at 35°C and centrifugation at 13 000 rpm (5 min).

2.4 | Calibration curves based on isotope dilution and standard addition

Acetyl-L-carnitine at different concentrations was added to plasma and vortexed for 30 seconds, followed by addition of CHCA solution. A volume of 0.40 µL of this mixture was pipetted into the channels and dried under ambient environments.

For calibration, standard solutions of acetyl-L-carnitine at 0.50 µM, 1.00 µM, 2.00 µM, 5.00 µM, 10.00 µM, 20.00 µM, 37.50 µM, and 50.00 µM were used. Calibration curves were obtained by using a combined standard addition/isotope dilution method as described by Lee et al, to improve accuracy and precision[15]: $y = b \times (c_{sample} + x)$, where y = isotope ratio IR_{sample}, $b = k \times / (c_{is,sol} \times V_{is,\ sol}/V_{sample})$ and $x = (V_{s,sol} \times c_{s,sol})/V_{sample}$. k is the response factor of the instrument. In our experiments, $c_{is,sol}$, $V_{is,sol}$, and V_{sample} were always invariant; therefore, both b and k were constants; c_{sample} = concentration of native acetylcarnitine in the sample, IR_{sample} = intensity ratio of acetylcarnitine to d_3-acetylcarnitine, $c_{is,sol}$ concentration of standard d_3-acetylcarnitine solution, $V_{is,sol}$ volume of standard d_3-acetylcarnitine solution, V_{sample} volume of sample, $V_{s,sol}$ volume of standard acetylcarnitine solution, and $c_{s,sol}$ concentration of standard acetylcarnitine solution. The sample concentration (c_{sample}) was obtained from the negative x intercept value by plotting experimental data as y versus x after least-squares fitting. An 8-point calibration curve was used (with 10 technical replicates at each concentration level). As a comparison, the calibration curve of acetyl-L-carnitine from a conventional smooth stainless-steel target plate was used, with identical concentrations as those used on the channel target plate.

2.5 | Evaluation of matrix effects

To evaluate matrix effects, a calibration curve of acetylcarnitine from spiked pure solvent (water) was used, with identical concentrations as those used in human plasma. We assessed plasma matrix effects by comparing the signals of acetyl-L-carnitine in water with that in plasma. The relative ratio of the slopes b_{serum}/b_{water} was used as indicator for matrix effects.

2.6 | Trueness and precision

For trueness evaluation, 3 three quality controls (1.00 µM, 5.00 µM and 20.00 µM) were incorporated into each calibration curve and measured five times.

Precision was assessed by repeatability (intraday) and intermediate (interday) precision. Precision was determined from five same-day

replicates and daily measurements over a period of 5 days. The results were expressed as % RSD.

2.7 | MALDI channel plates and sample preparation

Custom channel plates were made in the university workshop using commercial stainless steel plates (Figure 1). Length, width, and depth of the channels were 3.0, 0.35, and 0.40 mm, respectively.

2.8 | Mass spectrometry

MS experiments were performed with a Brucker Esquire HCT+ 3-D ion trap (Bremen, Germany) coupled with a MassTech (Burtonsville, Maryland) atmospheric pressure MALDI source. An Nd:YAG laser with wavelength of 355 nm was used as the light source. Laser energy was set to 50% and repetition rate at 200 Hz. Mass spectra were acquired in positive ionization mode. The mass spectrometer was set to smart mode with drying gas temperature at 300°C and flow rate at 5.0 L/min. Acetyl-L-carnitine and d_3-acetyl-L-carnitine were detected in multiple reaction monitoring (MRM) using a relative collision energy of 0.50. Two transitions per analyte were monitored, viz, m/z 204 → 145 and 204 → 85 for acetyl-L-carnitine, and m/z 207 → 145 and 207 → 85 for the d_3 isotope standard. For data acquisition, horizontal rastering was used to cover the entire sample area for each channel at a speed of approximately 40 mm/min, resulting in 30-second-long signal profiles per sample channel (approximately 6000 laser shots were averaged per channel; individual data points along the channel were acquired for 4 s in 0.4 mm steps; data acquisition started 0.25 mm before each channel and stopped 0.25 mm after).

2.9 | SEM and light microscope images

The morphologies of CHCA/acylcarnitine co-crystals within the channels and on the surface of the conventional target plates were characterized by secondary electron microscopy (DEI Quanta 400, Hillsboro, Oregon) and Moticam 3.0 (Motic Deutschland, Wetzlar, Germany).

3 | RESULT AND DISCUSSION

In this study, we introduced a new target plate with customized channels to improve sample homogeneity and reproducibility in quantitative MALDI-MS. As shown in Figure 1, the channels were milled into the center of the sample spots of a regular MALDI plate, giving an 8 × 12 matrix of 96 channel wells. The length, width, and depth of each of the cuboid channels were 3.0, 0.35, and 0.40 mm, respectively. The width was marginally narrower than the diameter of the used laser beam, which was 0.40 mm, making sure that the beam covered the entire width of the channel, while the beam was moved along the length of the channel during data acquisition.

We used acetyl-L-carnitine in human plasma as analyte to demonstrate the abilities of the new plate. Acylcarnitine is an essential endogenous metabolite in mammals, usually at concentration levels in the range of 3 to 14 μmol/L in plasma.[16-18] As the metabolism of acetyl-L-carnitine is closely linked to a variety of metabolic problems, it is routinely monitored in clinical diagnostics, usually by using LC-MS techniques. As LC-MS methods typically include a time-consuming chromatography step, MALDI-MS was investigated here as a potentially faster alternative to LC-MS.[19] It has been previously demonstrated that MALDI-MS provided quantitative abilities comparable with ESI-based LC-MS/MS for pharmaceutical drugs and biological fluids,[20-22] with comparable analytical figures of merit, but analysis times of up to 100 times faster.

3.1 | Comparison between channel and conventional target plates

The most desired feature of the new channel plate was to improve the quantitative reproducibility of MALDI analysis, by introducing constant volumes of sample and matrix solution into each of the well-defined channels and by illuminating the entire sampling surface with the laser light. In order to fill the channels with a well-defined, constant amount of sample solution, a 0.4 μL of the sample solution was pipetted into the channels (Figure 2A). The solutions spontaneously and evenly distributed within the channels by means of capillary action (a short video clip of this procedure is shown in the Supporting

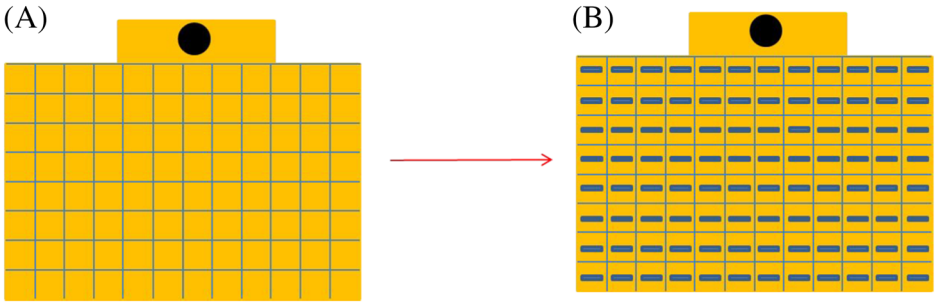

FIGURE 1 Schematic diagram of the MALDI target plates: (A) original target and (B) customized channel target. The channel size is as follows: length, 3.00 mm; width, 0.35 mm; depth, 0.40 mm. Matrix is added to channels using capillary action, and the analytes are added using a micropipette

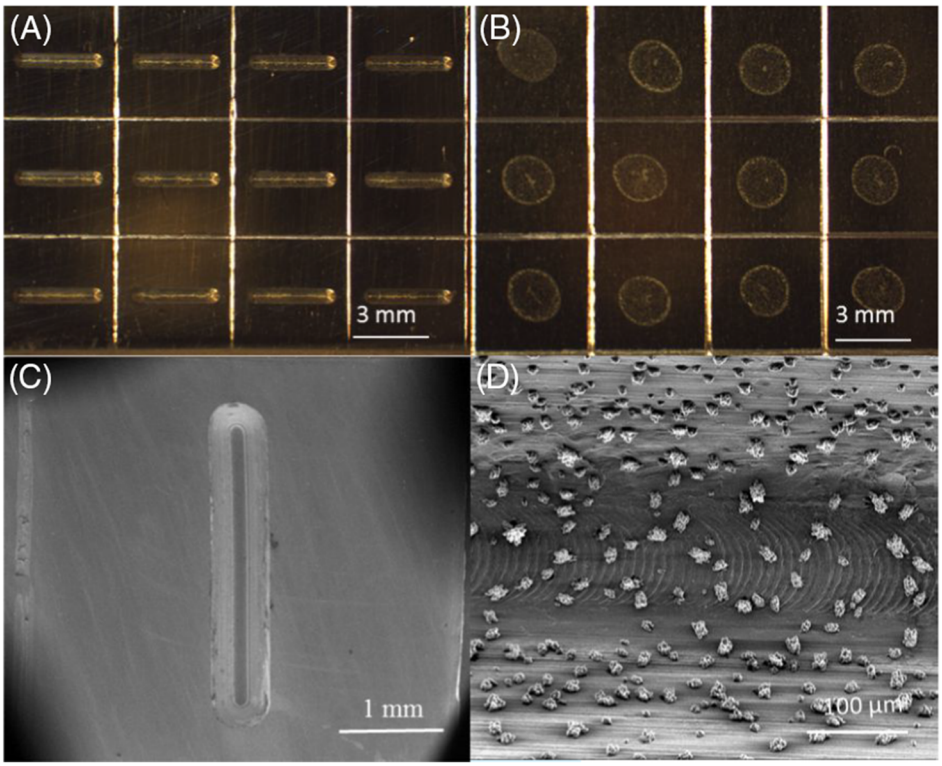

FIGURE 2 Light microscope images of samples on (A) channel plates and (B) smooth conventional stainless steel MALDI plates. (C) and (D) are scanning electron microscopy (SEM) images of sample/matrix mixtures deposited into the channels at different magnification levels [Colour figure can be viewed at wileyonlinelibrary.com]

Information, with added methyl orange dye to improve visibility). As the solvent evaporates, co-crystals of analytes/matrix readily formed within the channels without the possibility for a coffee ring effect, similar to the forced co-crystallization of analyte/matrix on hydrophobic surfaces.[7,13] For comparison, the same solution was pipetted onto a conventional stainless-steel target plate, resulting in the well-known coffee ring effect (Figure 2B).

The homogenous nature of the sample matrix crystals within channels, without any coffee ring formation, was further illustrated at higher magnifications using SEM (Figures 2C,D). According to Wong et. al, there is a minimal size for coffee ring structures for different materials.[23] The authors point out that for suspended particles of about 100nm size, the minimum diameter of the coffee ring structures is around 10 µm. In our channels, the surface is very rough, effectively dividing the channel surface into smaller subcompartments of few micrometers size or even smaller. We hypothesize that these small compartments are individually filled with CHCA and acetyl-L-carnitine crystals, preventing the formation of coffee ring structures in the channels such as those seen on the smooth regular steel surfaces.

3.2 | Reproducibility

Under optimized MALDI-MS/MS condition, we evaluated the reproducibility of the acetyl-L-carnitine signal produced from different channels across the plate. A plot of relative intensity (analyte/internal standard) of acetyl-L-carnitine from 10 different channels is shown in Figure 3. The relative standard deviation in these experiments was less

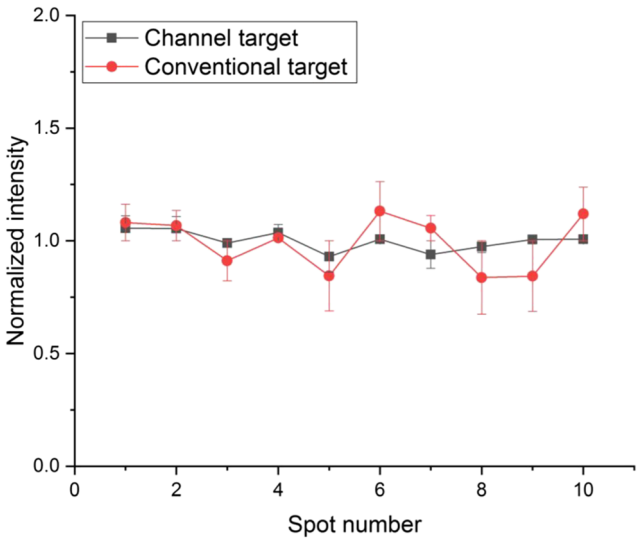

FIGURE 3 Reproducibility of measurement of acetyl-L-carnitine across 10 different samples from a channel plate in comparison with a conventional plate at equal concentration levels (analyte and internal standard, 20.00 µM each). The intensity ratio of acetyl-L-carnitine to d_3-acetyl-L-carnitine was normalized and displayed on the *y* axis [Colour figure can be viewed at wileyonlinelibrary.com]

than 5.9%. In comparison, the relative standard deviation from a conventional target plate was 15.6%.

The improved signal reproducibility largely resulted from the complete consumption of the sample/matrix crystals within the channels, which effectively removed sweets spots issues. Complete laser ablation during quantitative MALDI has previously been shown to greatly improve precision.[2,13] In our experiments, the channels were 0.35 mm wide, while the laser beam's diameter was slightly larger, viz, 0.40 mm, thus enabling the entire width of the channel to be irradiated.

3.3 | Calibration curves

Standard addition method is commonly used to quantify endogenous compounds in complex biological samples, when no blank sample matrix is available. Here, we used this technique for the quantification of acylcarnitine in human plasma. The calibration curve was obtained by plotting the intensity ratio of acetyl-L-carnitine to d_3-acetylcarnitne against the added concentration (Table 1). In comparison, a calibration curve of acetyl-L-carnitine from a conventional smooth target plate was used. Table 1 clearly shows, however, that all investigated analytical figures of merit obtained from the channel plate were superior to the conventional plate.

3.4 | Limits of quantification

LOQ was defined as the lowest concentration from the calibration curves that could be readily quantified with a precision of 20% RSD or better. From our experiments, the LOQ of acylcarnitine from the channel target plate was 0.50 μM, which was twofold lower than the LOQ from the conventional plate (Table 1).

3.5 | Matrix effects

We evaluated the effect of the plasma matrix by comparing the relative signal intensities in plasma and in pure solvent (water). The resulting calibration plots are illustrated in Figure 4. The slopes for acetyl-L-carnitine from plasma and water were 0.046 and 0.040, respectively. These values were used as indicators for matrix effects as described in experimental part. From these results, it could be seen

TABLE 1 Quantification results for acetyl-L-carnitine using the standard addition method on both channel and conventional target plates

Target Plate	Spiked Concentration, μM	$y = b \times c_{sample} + bx$	R^2	LOQ, μM[a]
Channel target	0.50-50.00	$y = 0.189 + 0.046x$	0.9989	0.50
Conventional target	0.50-10.00	$y = 0.226 + 0.043x$	0.9798	1.00

[a]LOQ was defined as the lowest concentration that could be quantified with a precision of 20% RSD or better.

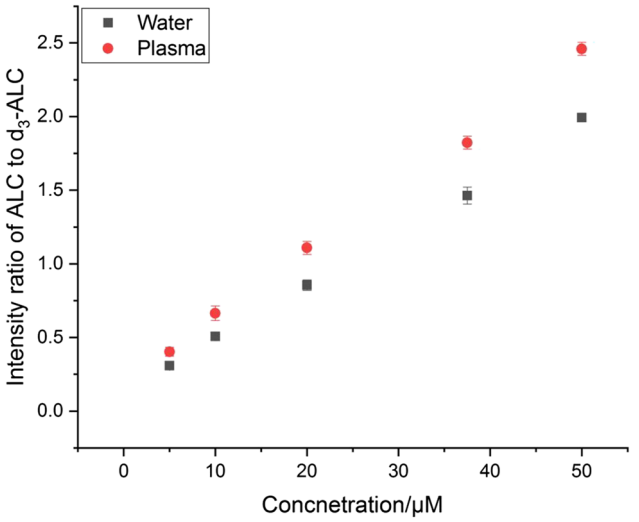

FIGURE 4 Calibration plots from spiked plasma and pure solvent (water). The concentration of d_3-acetyl-L-carnitine was 20.00 μM [Colour figure can be viewed at wileyonlinelibrary.com]

that the matrix strongly influenced the acetyl-L-carnitine signal in plasma, requiring a combination of the standard addition method and isotope dilution analysis for correction.

3.6 | Human samples

Samples from two volunteers were analyzed using the developed method, and concentrations levels of 4.11 μM and 8.48 μM were determined (Table 2), which are comparable with levels typically seen in other studies.[16]

3.7 | Trueness and precision

Trueness was assessed by analyzing quality control samples at low, medium, and high concentration levels in plasma (Table 3). The

TABLE 2 Measurement precision in human plasma using the standard addition method

	AC concentration, μM	Intraday (RSD, %)	Interday (RSD, %)
Sample 1	4.11	3.72	4.0
Sample 2	8.47	2.86	6.0

TABLE 3 Recovery rates at three different concentrations in plasma

Spiked Concentration (μM)	Detected Concentration, μM (RSD, %)	Recovery, %
1.00	1.07 (7.94)	107.0
5.00	4.91 (5.74)	98.2
20.00	20.63 (3.11)	103.2

recovery rates for each concentration were in range of 98.2% to 107.0% with RSD less than 8.0%. Precision was determined from intraday and interday experiments, ranging from 2.9% to 6.0%, respectively (Table 2).

4 | CONCLUSIONS

We have developed a simple technique to produce homogenous crystals of matrix and sample using a novel channel sampling plate for MALDI-MS. The channel design afforded very good reproducibility of the measurements across different sample spots, while at the same time improving detection sensitivity over regular MALDI plates. The applicability of the new plates was demonstrated by developing a quantitative assay for the measurement of acetyl-L-carnitine in human plasma. The new technique is inexpensive, does not require specialized sample deposition techniques, and has the potential for full automation and thus high throughput quantitative measurements.

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ORCID

Peng Zhang https://orcid.org/0000-0003-1695-360X
Dietrich A. Volmer https://orcid.org/0000-0003-2820-1480

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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